EXHIBIT 1

Changes in Plasma Lipids During Renin–Angiotensin System Blockade by Combination Therapy (Enalapril Plus Valsartan) in Patients With Diabetes and Hypertension

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Abstract: There is experimental evidence of an interaction between the angiotensin system and lipid metabolism. The aim of this study was to evaluate whether a block of the angiotensin system achieved both by ACE inhibition and angiotensin II–AT1 receptor blockade could affect the plasma lipid profile and, if so, what relationship exists between these possible changes and glucose metabolism and blood pressure. In 50 patients with type 2 diabetes and hypertension, treated with diabetes drugs and enalapril, we evaluated the glycemic and lipid profile together with the HOMA insulin-resistance index, blood pressure and microalbuminuria at baseline and 3 months after the addition of valsartan. At the second evaluation, blood pressure was reduced as expected, whereas the glycemic profile, the HOMA index, and the body mass index were unchanged. Total cholesterol, LDL-c, and apoprotein B were reduced during combination therapy ($P = 0.003$, $P = 0.001$, and $P = 0.004$, respectively), plasma HDL-c was slightly though significantly increased ($P = 0.024$), whereas apoprotein A and triglyceride levels did not change. After adjustment for the insulin resistance index and for blood pressure, the reduction of LDL-c and apoprotein B and the increase in HDL-c remained significant. The variation in lipid profile was not related to the changes in blood pressure. Moreover, the addition of valsartan to enalapril was associated with a reduction in microalbuminuria, which remained significant after adjustment for LDL-c or blood pressure changes. Thus, the greater degree of renin–angiotensin system blockade or specific pharmacodynamic effects of valsartan could account for the changes in plasma lipid profile observed in this study.

Key Words: angiotensin, lipid metabolism, type 2 diabetes, valsartan, enalapril

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Atherogenesis is characterized by complex phenomena among which the renin–angiotensin system (RAS) is now recognized as an important modulating factor. The key role of low-density lipoproteins (LDL) and their modified forms in determining the vascular cell dysfunction and injury is well known.[1,2] Recently there has been increasing evidence of an interaction between hyperlipidemia and the RAS activation. LDL up-regulates AT1 receptor expression,[3,4] and, conversely, angiotensin II up-regulates specific endothelial LOX-1 receptors for ox-LDL through AT1-receptor activation and facilitates oxidation of LDL and its uptake by monocytes/macrophages (among the reported mechanisms involved in this process are an increment in cellular proteoglycan content and fucoidin-binding receptors and increased cellular CD36 mRNA expression).[5–10] Moreover, recent experimental evidence in hypertension has linked the modifications associated with the atherogenesis occurring in vascular walls and plasma with both the lipid profile and metabolism and the angiotensin system. The SHR animal model, which shows increased angiotensin II levels, renin activity, angiotensin receptors, and angiotensinogen mRNA, exhibits an up-regulation of the LOX-1 receptor for ox-LDL expression.[11,12] Moreover, LDL derived from hypertensive patients is more susceptible to lipid peroxidation than LDL derived from normotensive controls.[12] Diabetes mellitus magnifies the risk of cardiovascular damage and leads to accelerated atherosclerosis.[13] Various elements such as dyslipidemia, hyperglycemia, insulin resistance, and platelet activation and aggregation, together with the increased prevalence of hypertension, cooperate in the increase of cardiovascular morbility and mortality in patients with diabetes.[13] In addition, microalbuminuria has been shown to be an independent predictor of increased cardiovascular risk in diabetic patients.[14] The aim of this study was to evaluate in this high-risk group of patients with diabetes and hypertension whether a greater blockade of the RAS achieved by inhibiting the system both at the converting enzyme and at the AT1 receptor levels could affect the plasma lipid profile and, if so, what relationship exists between these possible changes and changes in glucose metabolism and blood pressure. As a secondary endpoint we investigated whether microalbuminuria, an index of microvascular damage, could be reduced by the addition of valsartan to enalapril and whether this possible change was accounted for by blood pressure or lipid profile variations.

METHODS

We studied 62 consecutive patients with both type 2 diabetes and hypertension[15] referring to our Hypertension

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Center with the following characteristics: all were treated with enalapril 10 mg/d for hypertension and with diet and/or antidiabetic medications for diabetes (4 patients with diet therapy, 11 with biguanides, 10 with sulfonylureas, 26 with biguanides and sulfonylureas, 8 with biguanides and sulfonylureas and acarbose, and 3 with insulin). Moreover, the patients were included in the study if clinical blood pressure was greater than 130/80 mm Hg despite the enalapril treatment and the clinical condition did not require a change in diet and/or antidiabetic medications.

In 50 patients (group 1) valsartan 80 mg/d was added to the drugs already taken (enalapril and antidiabetics). Twelve consecutive patients (control group: group 2) agreed to continue the antihypertensive treatment with enalapril alone for the following 3 months.

All the patients were evaluated twice (at baseline and after 3-month follow-up) with clinical visits including calculation of body-mass-index (BMI), measurements of sphygmomanometric blood pressure, evaluation of ambulatory blood pressure, and laboratory examinations. In addition, the 24-hour microalbuminuria was measured at both examinations.

In all subjects, blood sampling was obtained to determine the glycemic profile (fasting glucose, fasting insulin, Hb_{A1c}), total cholesterol, HDL-c, LDL-c, triglycerides, apoprotein A, apoprotein B. The homeostasis model assessment of insulin resistance (HOMA-IR) index was calculated according to the formula: HOMA-IR index = [fasting insulin (pmol) × fasting glucose (mmol/L)]/22.5.[16]

Blood Pressure Evaluations

Sphygmomanometric blood pressure was determined in the morning between 9:00 and 10:00, and systolic blood pressure, diastolic blood pressure, and pulse pressure (arithmetic difference between systolic and diastolic measures) were considered in subsequent analyses. Afterward a 24-hour blood pressure monitoring was performed. The subjects were previously instructed to take the antihypertensive treatment (enalapril 10 mg) at 7:00 AM, even on the days of the visits. Then the patients were instructed to provide 24-hour urines for microalbuminuria detection and were submitted to a fasting blood sampling. The blood pressure monitoring was performed with a Takeda 2430 (A&D Co) monitor set to take a measurement every 15 minutes. The 24-hour systolic and diastolic blood pressures were evaluated. After 3 months all the subjects again underwent a sphygmomanometric evaluation of blood pressure, 24-hour ambulatory blood pressure monitoring, and blood sampling. Microalbuminuria was also measured at 3-month follow-up. All subjects took medications regularly, taking antihypertensive drugs at 7:00 AM even on the day of the test (50 patients, enalapril 10 mg plus valsartan 80 mg; 12 patients, enalapril 10 mg).

Statistical Analysis

Data are presented ± SD, unless skewed when median and interquartile range (IQR) were reported. A χ^2 test was used to compare the prevalence of the various treatments for diabetes (diet, oral antidiabetic treatment, insulin) in the 2 groups of patients (group 1, patients in whom antihypertensive treatment was increased to enalapril plus valsartan after the first evaluation; group 2, patients who stayed on enalapril alone).

The Mann-Whitney *U* test was performed to compare hemodynamic and metabolic parameters between group 1 and group 2. A general linear regression model was fitted to the data to assess changes over time of blood pressure, lipid profile, and (log-transformed) microalbuminuria, with calculation of Huber-White robust standard errors to account for intrapatient correlation in time. The observed changes were also controlled for insulin resistance and blood pressure or lipid profile in a multivariate model. Pearson correlation coefficient was computed to measure the association between changes in blood pressure and in lipid profile. Stata 7 (StataCorp, College Station, TX) was used for computation. A 2-sided P value <0.05 was retained for statistical significance.

RESULTS

In 50 type 2 diabetic patients whose antihypertensive treatment was increased after the first evaluation adding valsartan to enalapril (group 1), the lipid profile was significantly changed after a 3-month follow-up. During combination therapy, total cholesterol, LDL-c, and apoprotein B levels were reduced by 16 mg/dL, 14 mg/dL, and 10 mg/dL, respectively, when compared with the values observed at the first evaluation, whereas the plasma HDL-c was slightly though significantly increased by 2 mg/dL (Table 1). Figure 1 shows the individual changes in LDL-c and in HDL-c. The apoprotein A and triglyceride levels did not significantly differ from the values found at the first evaluation (Table 1).

In these group 1 patients, the glycemic profile and the insulin-resistance HOMA-IR index at the follow-up examination were similar to those found at the first evaluation, but the sphygmomanometric blood pressure as well as the 24-hour ambulatory blood pressure were significantly reduced as expected by the addition of valsartan to enalapril (Table 1). Moreover, the body-mass index did not change after the 3-month follow-up (first evaluation, group 1, 26.8 ± 4.8 kg/m^2; second evaluation, group 1, 26.5 ± 4.6 kg/m^2).

At baseline (enalapril monotherapy in both groups), the lipid profile, the glycemic profile, and the HOMA-IR index were similar between group 1 and group 2 (12 patients who stayed on enalapril alone in the following 3 months) (Table 1). Moreover, the body-mass index was similar between the groups (group 2, 26.9 ± 4.8 kg/m^2), and the prevalence of dietary treatment and/or oral antidiabetic drugs and/or insulin treatment was similar in the 2 groups of patients. The clinical blood pressure, pulse pressure, and metabolic profile in group 1 did not differ from those in group 2 (Table 1). These patients did not show any statistically significant change in lipid and glycemic profile, HOMA-IR index, or body-mass index during the follow-up period (data not shown).

In group 1 patients who showed an improvement in lipid profile after combination therapy, after adjustment for insulin resistance index and for blood pressure, the reduction of LDL-c and apoprotein B and the increase in HDL-c remained significant and did not change in magnitude (adjusted differences: reduction of 13.6 mg/dL, reduction of 10.4 mg/dL, and increase of 3.9 mg/dL, respectively). The variation in lipid profile

TABLE 1. Lipid Profile, Glycemic and Metabolic Parameters, and Blood Pressure Values in Group 1 (Patients Who Added Valsartan to Enalapril During the 3-Month Follow-up) and in Group 2 Patients (Subjects Who Remained on Enalapril Alone)

	Group 1			Group 2
	Baseline* (Enalapril)	Follow-up (Enalapril + Valsartan)	P	Baseline* (Enalapril)
Lipid profile				
Total cholesterol (mg/dL)	220.9 ± 44.9	205.5 ± 35	0.003	224 ± 42
LDL-c (mg/dL)	134.6 ± 36	121 ± 31.1	0.001	137.4 ± 29
HDL-c (mg/dL)	50.5 ± 14.9	52.5 ± 15.3	0.024	51.12 ± 12
Apoprotein B (mg/dL)	114 ± 31	103.8 ± 22	0.004	117 ± 34
Apoprotein A (mg/dL)	139.1 ± 26.3	133.3 ± 28.5	ns	140.2 ± 30
Tryglicerides (mg/dL)	178.8 ± 109.7	160.5 ± 84.6	ns	172.52 ± 97
Glycemic and metabolic parameters				
Fasting glucose (mg/dL)	170 ± 45	160 ± 47	ns	165 ± 48
Fasting insulin (μU/mL)	13.1 ± 9.8	14 ± 16.6	ns	12.5 ± 11.3
HOMA-IR index	5.29 ± 4.25	5.49 ± 4.65	ns	5.05 ± 4.36
Blood pressure values				
Sphygmomanometric SBP (mm Hg)	151 ± 20	136 ± 23	<0.001	153 ± 20
Sphygmomanometric DBP (mm Hg)	84 ± 10	76 ± 13	0.002	84 ± 12
Sphygmomanometric PP (mm Hg)	67 ± 15	60 ± 16	<0.001	68 ± 16
24-hour SBP (mm Hg)	145 ± 15	139 ± 14	0.01	146 ± 17
24-hour DBP (mm Hg)	78 ± 7	75 ± 6	0.05	77 ± 8

*$P > 0.01$ comparing baseline values between groups 1 and 2 (Mann-Whitney u test).
SBP indicates systolic blood pressure; DBP indicates diastolic blood pressure; PP indicates pulse pressure; LDL-c indicates low-density lipoprotein-cholesterol; HDL indicates high-density lipoprotein-cholesterol.

was not related to the changes in blood pressure as indicated by the lack of relationship between the variations in LDL-c and systolic, diastolic and pulse pressure changes occurring after the 3-month follow-up (Pearson R ≤ 0.27, ns, in all cases).

Moreover, the addition of valsartan to enalapril was associated with a reduction of microalbuminuria [median (IQR) 5.9 (2.4–12) at first evaluation and 1.0 (0.6–2.9) at second evaluation, $P < 0.001$]. The changes observed in (log-transformed) microalbuminuria remained significant and of the same magnitude after adjustment for LDL or blood pressure changes.

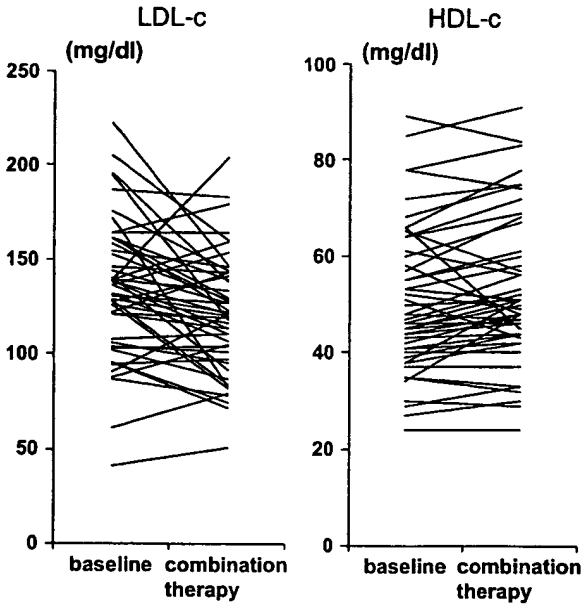

FIGURE 1. Changes in LDL-cholesterol ($P = 0.001$) and HDL-cholesterol ($P = 0.024$): baseline (enalapril) to combination therapy (enalapril plus valsartan).

DISCUSSION

Several experimental studies have suggested an interaction between dyslipidemia and the angiotensin system.[3–12] In rabbits a marked increase of AT1 receptor density has been shown in hypercholesterolemia.[4] In humans a close relationship has been found between AT1 receptor density and plasma LDL-cholesterol and the use of statins to lower cholesterol was associated with AT1 receptor down-regulation.[17] In this study we report in type 2 diabetic patients with hypertension that the greater inhibition of the RAS obtained with ACE inhibitors plus AT1 receptor blockade was associated with a significant reduction of LDL-cholesterol together with a reduction of apoprotein B and a slight though significant increase in HDL-c as well as the expected blood pressure lowering induced by the drugs.

Some reports on animals and in man have shown a reduction in LDL plasma levels or in cholesterol synthesis with RAS inhibition.[18–20] However, other studies have failed to find a lipid profile modification during ACE-inhibitor treatment.[17,21–24]

In humans, recently, a decrease in total cholesterol and LDL-cholesterol was seen in 60 hypertensive patients after a 12-week treatment with 80 mg daily valsartan, whereas no change in apoprotein B lipoprotein was observed.[25] Previously, significant decreases in total cholesterol, apolipoprotein B,

and apolipoprotein A have been seen during therapy with valsartan when compared with captopril in patients with type 2 diabetes mellitus and nephropathy.[26]

In our study, the improved lipid profile may be a result of the more complete block of the RAS obtained by using both enalapril and valsartan. Moreover, in the control group of patients who did not receive valsartan added to enalapril, no change was observed in lipid plasma levels.

Although a close interaction between the glucose and lipid metabolisms is well established, in our study glucose metabolism was unchanged in the patients who added valsartan to the previous treatment with enalapril, as indicated by similar Hb_{A1c} levels and glucose and insulin values. Moreover, similar body mass indices were found in these patients at the 2 evaluations. ACE inhibitors but not angiotensin II receptor antagonists seem to be associated with an improvement of insulin resistance[13,27]; in this study of diabetic hypertensives the HOMA-IR insulin resistance index was unchanged after the 3 months following the additional treatment with valsartan. In addition, changes in lipid profile were shown to be independent of insulin resistance and blood pressure in the multivariate model. Thus, it is not likely that insulin sensitivity could have accounted for the beneficial effects on the lipid profile seen in our study. However, it has to be acknowledged that we did not investigate insulin sensitivity with more sensitive methods.

Although the relative roles of AT1 and AT2 receptors in vascular remodeling are not completely clarified, most of the known vascular effects of angiotensin II are mediated through AT1 receptors, and their blockade has shown beneficial effects on atherogenesis. There is experimental evidence for an involvement of AT1 receptors in the cross-talk between lipid metabolism and angiotensin.[28–32] The lecitin-like receptor LOX-1 for ox-LDL is thought to participate actively in atherogenesis, and AT1-receptor blockade by losartan has been shown to decrease the enhanced LOX-1 expression up-regulated by both angiotensin II and high-cholesterol diet in vitro and in vivo.[6,31] Moreover, angiotensin II increases macrophage-mediated modification of LDL via a lipoxygenase-dependent pathway through AT1 receptors, and valsartan (but not AT2 receptor blockade) was shown to inhibit the lipoxygenase activity and, subsequently, the ability of the cells to modify LDL and the measured monocyte chemiotaxis.[32] Thus, in this study, the addition of valsartan to enalapril may have affected the lipid profile through the AT1 blockade. Moreover, in this study, the reduction of the renal damage expressed by microalbuminuria observed with valsartan remained significant after adjusting for blood pressure or LDL-c levels, possibly indicating a specific protective effect against microvascular injury as a result of using this drug, as already suggested by others.[33] Alternatively, a more prolonged follow-up may be needed to detect a potential relationship between renal protection and lipid metabolism changes.

Although not much is known about the local concentration of angiotensin II within the vascular wall, it has been suggested that locally generated angiotensin II may have autocrine and paracrine effects. The importance of tissue ACE activity in the interaction between the angiotensin system and lipid metabolism is shown by the relative difficulty in inhibiting tissue ACE activity compared with serum ACE levels, as a higher dose of ACE inhibitor is needed in vivo for the inhibition of neointimal formation.[34] The changes observed in the lipid profile could be ascribed, at least in part, to the action of valsartan at the vascular wall level.

CONCLUSION

The modulation of the lipid metabolism observed in our study may depend on the greater degree of block of the RAS obtained by combination therapy or on a specific pharmacodynamic effect of valsartan.

REFERENCES

1. Witzum JL, Steinberg D. Role for oxidized LDL in atherogenesis. *J Clin Invest*. 1991;88:1785–1791.
2. Aviram M. Modified forms of low density lipoprotein and atherosclesosis. *Atherosclerosis*. 1993;98:1–9.
3. Nickenig G, Sachinidis A, Michaelsen F, et al. Upregulation of vascular angiotensin II receptor gene expression by low density lipoprotein in vascular smooth muscle cell. *Circulation*. 1997;95:473–478.
4. Nickenig G, Jung O, Strehlow K, et al. Hypercholesterolemia is associated with enhanced angiotensin AT1 receptor expression. *Am J Physiol*. 1997; 272:H2701–H2707.
5. Li DY, Zhang YC, Philips MI, et al. Upregulation of endothelial receptor for oxidized low-density lipoprotein (LOX-1) in cultured human coronary artery endothelial cells by angiotensin II type 1 receptor activation. *Circ Res*. 1999;84:1043–1049.
6. Morawiets H, Rueckschloss U, Niemann B, et al. Angiotensin II induces LOX-1, the human endothelial receptor for oxidized low-density lipoprotein. *Circulation*. 1999;100:899–902.
7. Keidar S, Kaplan M, Hoffman A, et al. Angiotensin II stimulates macrophage-mediated oxidation of low density lipoprotein. *Atherosclerosis*. 1995;115:201–215.
8. Keidar S, Attias J. Angiotensin II injection into mice increases the uptake of oxidized LDL by their macrophages via a proteoglycan-mediated pathway. *Biochem Biophys Res Commun*. 1997;239:63–67.
9. Keidar S, Heinrich R, Kaplan M, et al. Angiotensin II administration to atherosclerotic mice increases macrophage uptake of oxidized LDL. A possible role for interleukin-6. *Atheroscler Thromb Vasc Biol*. 2001;21: 1464–1469.
10. Keidar S, Kaplan M, Aviram M. Angiotensin II-modified LDL is taken up by macrophages via the scavenger receptor, leading to cellular cholesterol accumulation. *Atheroscler Thromb Vasc Biol*. 1996;16:97–105.
11. Nagas M, Hirose S, Fujita T. Unique repetitive sequence and unexpected regulation of expression of rat endothelial receptor for oxidized low density lipoprotein (LOX-1). *Biochem J*. 1998;330:1417–1422.
12. Keidar S, Kaplan M, Shapira C, et al. LDL isolated from patients with essential hypertension exhibit increased propensity for oxidation and enhanced uptake by macrophages: a possible role for angiotensin II. *Atherosclerosis*. 1994;107:71–84.
13. Sowers JR, Epstein M, Frohlich ED. Diabetes, hypertension, and cardiovascular disease: an update. *Hypertension*. 2001;37:1053–1059.
14. Mattock MB, Morrish NJ, Viberti G, et al. Prospective study of microalbuminuria as predictor of mortality in NIDDM. *Diabetes*. 1992; 41:736–741.
15. The Seventh Report of the Joint National Committee on Prevention. Detection, evaluation, and treatment of high blood pressure. *JAMA*. 2003; 289:2560–2571.
16. Matthews DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. 1985;28:412–419.
17. Nickenig G, Baumer AT, Temur Y, et al. Dysregulated AT1 receptor function and density in hypercholesterolemic men. *Circulation*. 1999;100: 2131–2134.

18. Keidar S, Attias J, Heinrich R, et al. Angiotensin II atherogenicity in apoprotein E deficient mice associated with increased cellular cholesterol biosyntesis. *Atherosclerosis*. 1999;146:249–257.
19. Kowala M, Grove R, Aberg G. Inhibitors of angiotensin-converting enzyme decrease early atherosclerosis in hyperlipidemic hamster. Fosinopril reduces plasma cholesterol and captopril inhibits macrophage-foam cell accumulation independently of blood pressure and plasma lipids. *Atherosclerosis*. 1994;108:61–72.
20. Miyashita Y, Ito Y, Hasiguchi S, et al. Effect of temocapril hydrochloride on serum lipid levels in patients with hypertensive type 2 diabetes mellitus. *J Atheroscler Thromb*. 2001;8:25–29.
21. Thurig C, Bohlen L, Schneider M, et al. Lisinopril is neutral to insulin sensitivity and serum lipoproteins in essential hypertensive patients. *Eur J Clin Pharmacol*. 1995;49:21–26.
22. Alleman Y, Baumann S, Jost M. Insulin sensitivity in normotensive subjects during ACE inhibition with fosinopril. *Eur J Clin Pharmacol*. 1992;42:275–280.
23. Lerch M, Weidmann P, Ho MP, et al. Metabolic effects of temocapril in hypertensive patients with diabetes mellitus type 2. *J Cardiovasc Pharmacol*. 1999;33:527–533.
24. Bohlen L, Bienz R, Doser M, et al. Metabolic neutrality of perindopril: focus on insulin sensitivity in overweight patients with essential hypertension. *J Cardiovasc Pharmacol*. 1996;27:770–776.
25. Hanefeld M, Abletshauser C. Effect of angiotensin II receptor antagonist valsartan on lipid profile and glucose metabolism in patients with hypertension. *J Int Med Res*. 2001;29:270–279.
26. Cheung R, Lewanczuk RZ, Rodger NW, et al. The effect of valsartan and captopril on lipid parameters in patients with type 2 diabetes mellitus and nephropathy. *Int J Clin Pract*. 1999;53:584–592.
27. Fogari R, Zoppi A, Corradi L, et al. Ace-inhibition but not angiotensin II antagonism reduced fibrinogen and insulin resistance in overweight hypertensive patients. *J Cardiovasc Pharmacol*. 1998;32:616–620.
28. Singh BM, Mehta JL. Interactions between the renin–angiotensin system and dyslipidemia: relevance in the therapy of hypertension and coronary heart disease. *Arch Intern Med*. 2003;163:1296–1304.
29. Berry C, Touyz R, Dominiczak AF, et al. Angiotensin receptors: signaling, vascular pathophysiology, and interactions with ceramide. *Am J Physiol*. 2001;281:H2337–H2365.
30. Ferrario CM, Smith R, Levy P, et al. The hypertension–lipid connection: insight into the relation between angiotensin II and cholesterol in atherogenesis. *Am J Med Sci*. 2002;323:17–24.
31. Chen H, Li D, Sawamura T, et al. Upregulation of LOX-1 expression in aorta of hypercholesterolemic rabbits: modulation by losartan. *Biochem Biophys Res Commun*. 2000;276:1100–1104.
32. Scheidegger KJ, Butler S, Witztum JL. Angiotensin II increases macrophage-mediated modification of low density lipoprotein via a lipoxygenase-dependent pathway. *J Biol Chem*. 1997;272:21609–21615.
33. Viberti G, Wheeldon NM. Microalbuminuria reduction with valsartan in patients with type 2 diabetes mellitus. *Circulation*. 2002;106:672–678.
34. Rakugi H, Wang DS, Dzau VJ, et al. Potential importance of tissue angiotensin-converting enzyme inhibition in preventing neointimal formation. *Circulation*. 1994;90:449–455.